European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2001; 5: 59-63

Efficacy of a single-dose ondansetron for preventing post-operative nausea and vomiting after laparoscopic cholecystectomy with sevoflurane and remifentanil infusion anaesthesia

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Abstract. – **In this randomized study we compared the efficacy of ondansetron 4 mg with ondansetron 8 mg for the prevention of postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy with sevoflurane and remifentanil infusion anaesthesia. Sixty patients were randomized to receive ondansetron 8 mg (30 pts) or ondansetron 4 mg (30 pts) before the induction of anaesthesia with thiopental and remifentanil. Anaesthesia was maintained with sevoflurane (0.5 MAC), oxygen and remifentanil infusion (0.25, 0.35, 0.5 µg/kg/min). Postoperative analgesia was provided by intravenous ketorolac 60 mg. The incidence of PONV, the pain score, and the analgesic requirement were recorded for 24 hours. There was no difference among groups in patient characteristics, risk factors for PONV, or side effects. During the first 6 h postoperatively, the incidence of PONV after ondansetron 4 mg and 8 mg were similar ($p < 0.001$). After 6 h the incidence of PONV increased significantly in patients who had received ondansetron 4 mg ($p = 0.01$) and was greater than that in patients who had received ondansetron 8 mg ($p = 0.001$). We conclude that single-dose ondansetron 8 mg is more effective than ondansetron 4 mg in the prevention of PONV after laparoscopic cholecystectomy. This surgery is associated with a high incidence of postoperative nausea and vomiting. A single dose of IV ondansetron 8 mg is well tolerated and decrease the number of nausea and vomiting episodes after surgery.**

Key Words:

PONV, Remifentanil, Laparoscopic cholecystectomy, Anaesthesia.

Introduction

Laparoscopic cholecystectomy is associated with shorter post-operative hospital stay, less post-operative pain, and has become a widely used surgical technique[1,2]. It has been reported that the incidence of nausea and vomiting is as high as 25-72% following laparoscopic cholecystectomy[3,4]. Ondansetron is a selective 5-hydroxytryptamine[3] receptor antagonist with potent antiemetic activities. Its elimination half-time is 3.2-3.9 hours and a single dose of ondansetron may provide prolonged antiemetic effects. Ondansetron is effective in preventing postoperative nausea and vomiting (PONV) after laparoscopic cholecystectomy, and orthopedic, gynecologic, thyroid, and ophtalmic surgery. The recommended dose for PONV prophylaxis is a single 4-mg bolus of IV ondansetron[5].

However the emetic stimuli after surgery may be conditioned also by the anaesthetic drugs used and by the respective doses, so in randomized study we compared the efficacy and safety of ondansetron 4 mg with ondansetron 8 mg for the prevention of PONV after laparoscopic cholecystectomy with sevoflurane and remifentanil infusion anaesthesia.

Methods

The study was approved by the our clinical research Ethics Committee. Written informed consent was obtained from all patients.

We studied 60 patients submitted laparoscopic cholecystectomy (32 male, 28 female; mean age 44 ± 9 years). All patients were ASA physical status I or II. Patients were ex-

cluded if they had preexisting nausea or vomiting or had received opioids or drugs with known antiemetic properties in the 24 hours before surgery. Patients with a history of esophageal reflux or opiod or alcohol abuse were also excluded. All patients were interviewed during the preoperative assessment. A history of motion sickness and PONV was noted. Preoperative electrocardiogram, full blood counts and renal and liver function test were performed. The patients were premedicated with diazepam and fasted from midnight before surgery.

In the operating room, routine monitoring was applied. Patients were assigned randomly to receive either ondansetron 8 mg or ondansetron 4 mg. Study drugs were prepared by an anaesthesiologist not otherwise involved in the study and were injected IV over 30 s. Arterial pressure and heart rate were recorded noninvasively every 5 minutes. Adverse reactions, including pain on injection, signs of allergy, dizziness, and chest or abdominal discomforts, were specially sought.

Anaesthesia was induced with remifentanil 1 µg/kg and thiopental 3-5 mg/kg. Vecuronium 0.1 mg/kg was administrated to facilitate tracheal intubation. All the patients were ventilated with a mixture O_2 and air (FiO_2 50%) and a respiratoriy rate of 12-15 with $ETCO_2$ about 35 mmHg. Anaesthesia was maintained with sevoflurane at end-tidal 1.1% and remifentanil infusion. The patients were randomly allocated to one of 3 groups to receive a maintenance infusion rate of 0.25 µg/kg/min, 0.35 µg/kg/min and 0.5 µg/kg/min. Perioperative analgesia was provided by IV ketorolac 60 mg administered before the end of the surgery.

At the end of surgery, anaesthesia was discontinued and residual neuromuscolar blockade was antagonized by using neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg). The trachea was extubated when the patient became fully awake. Anaesthetic time was defined as the start of the induction to the time when sevoflurane and remifentanil was discontinued. The subsequent period until the patient responded to verbal command was recorded as the recovery time.

Postoperatively all patients were monitored in the postanaesthesia care unit for 1 hour, after which time the patient returned to the ward. The incidence of nausea and emetic episodes (retching or vomiting), as well as the severity of nausea, pain, and sedation were recorded at 30-min intervals for 2 hours and then every 6 hours for the next 24 hours. Patients interviews were conducted in a standardized fashion by trained nurses who were blinded to the study drug. Retching or vomiting separated by at least 1 min was considered as separate emetic episodes. Adverse reactions were also recorded. Preoperative laboratory tests and electrocardiogram were repeated at 24 h.

Data Analysis

Categorical data were compared among groups using χ^2 analysis, and continuous data were analyzed by using the Kruskal-Wallis test. Intergroup differences were compared by using Fisher's exact test or the Mann-Whitney U-test. Severity of nausea during the initial 6 h was assessed by adding the nausea scores at 2h and 6 h postoperatively. Similarly the sum of the nausea scores at 12 h and 18 h indicated the severity 6-18 h postoperatively. The aggregate totals during these two periods were then compared among groups using the Kruskal-Wallis test. A complete response was defined as no nausea, emetic episodes, or rescue antiemetic during the entire 48 h observation. The time to the first nausea or emetic episode was calculated using Kaplan-Meier analysis and was compared among groups using the log-rank test. The effects of variables that may influence the incidence of PONV were analyzed by Cox regression. A paired t-test was used to compare the hemodynamic variables before and after injection of the study drugs. A P value < 0.05 was considered significant.

Results

Age, weight, height and variables that may influence PONV did not differ among the groups. A complete response was observed in 36.6% of patients in the ondansetron 4 mg group ($p = 0.001$) and in 86.6% of the ondansetron 8 mg group ($p < 0.001$). The medi-

an time to the first PONV episode was shorter in the ondansetron 4 mg group 12 (9-22.5) hours ($p < 0.001$) compared with that in the ondansetron 8 mg group, > 18 hours ($p < 0.001$). Both ondansetron 4 and 8 mg were effective in preventing emesis during the first 12 hours ($p < 0.001$). The incidence of emesis in patients who received ondansetron 4 mg increased significantly 6-18 h post-operatively compared with the initial 6 h ($p < 0.01$). In these 12 h, there were more emetic episodes in the ondansetron 4 mg compared with the ondansetron 8 mg group ($p < 0.001$). Rare and not significant emetic episodes among groups were recorded after the first postoperative day (Table I).

Nausea was also common during the first 20 h after surgery, but the overall severity was low. In the first 6 hours after surgery the median (range) aggregated nausea score in the ondansetron 4mg group, 6 (0-13), was significantly greater than that in the ondansetron 8 mg group, 0 (0-11) ($p < 0.001$). Despite an increase in the incidence of nausea score in the ondansetron 4 mg group remained low, 0 (0-18). This was similar to the score in the ondansetron 8 mg group, 0 (0-15) ($p = 0.15$).

During the entire 24-h study period, 3 patients who received ondansetron 4 mg ($p = 0.02$) and 1 of the 8 mg group (n=1; $p < 0.001$), required a rescue antiemetics therapy (methoclopramide 10 mg i.v.). Furthermore, 1 of the patients in the ondansetron 4 mg group who required rescue antiemetics continued to experience PONV and received 2 or more rescue treatments, whereas none in 8 mg group required a second dose.

There was no difference in pain scores among the groups. There was no adverse events during the injection of ondansetron. Arterial blood pressure and heart rate did not change after drug administration. Biochemical test were not different from preoperative values. One patient in the ondansetron 4 mg group complained of dizziness and an another in the same group had a mild headache during the early postoperative hours. No other adverse effects was noted.

Discussion

Patients undergoing elective laparoscopic cholecystectomy have a relatively high incidence of PONV (25-72%)[4]. This problem is multifactorial in origin, including the patient demographics, the nature of the underlying disease, the duration of surgery, anaesthetic technique and post-operative care[6]. The main patient-related factors are age, sex, obesity, and history of motion sickness and/or previous PONV. Surgical factors also include the effects of intraperitoneal CO_2 insufflation on residual stretching and irritation of the peritoneum[7]. In our randomized trial, however, the treatment groups were comparables with respect to patient demography, type of surgery, anaesthetic drugs administered and ketorolac used postoperatively. Therefore, the difference in the incidence of PONV in the groups is likely due to the differences in the dose of agents administered. We administered ondansetron immediately before the induction of anesthesia to maximize its potential preemptive antiemetic

Table I. Incidence of PONV during 24 hours for each study group.

Time	Drug	0.25 µg/kg/min	0.35 µg/kg/min	0.50 µg/kg/min
0-2 hours	Ondansetron 4 mg	1 pt* ≈	1 pt*	1 pt*
	8 mg	None*	None*	1 pt*
2-6 hours	Ondansetron 4 mg	2 pts* ≈	1 pt* ≈	None* ≈
	8 mg	None*	None*	None*
6-12 hours	Ondansetron 4 mg	1 pt* ≈	2 pts* ≈	1 pt* ≈
	8 mg	None*	1 pt *	None*
12-18 hours	Ondansetron 4 mg	1 pt ≈	1 pt ≈	1 pt ≈
	8 mg	1 pt	1 pt	1 pt
18-24 hours	Ondansetron 4 mg	None	None	None
	8 mg	1 pt	1 pt	None

* $p < 0.001$; ≈ $p < 0.01$.

effect. Scuderi and coll.[2] demonstrated that there is a difference in outcomes when routine antiemetic medication with ondansetron is administrated versus simply treating PONV when the symptoms occur. Moreover, Scholz and coll.[8] demonstrated that the ondansetron reduces the incidence of PONV in patients undergoing laparoscopic cholecystectomy as well as major gynaecological surgery. The precise mechanism of action of ondansetron in the reduction of the incidence of PONV is not known, but it has been suggested that it may act on sites containing 5-HT3 receptors with demonstrated anti-emetic effects.

Our data do not support the use of a smaller dose of ondansetron for PONV. The antiemetic effect of the ondansetron 4 mg was shorter than that of ondansetron 8 mg. A single IV dose of ondansetron 4 mg failed to decrease the incidence of PONV 6 h postoperatively. In our study the ondansetron 8 mg is the dose effective to reduce and/or get rid off PONV. In fact, complete response was observed in the ondansetron 8 mg study group (86.6%) and 4 mg group (36.6%).

The study also showed that only 1 patient of 8 mg group required rescue antiemetics compared with 3 patients of 4 mg group. Furthermore, 1 of the 3 patients in the ondansetron 4 mg group who required rescue antiemetics continued to experience PONV and received 2 or more rescue treatments, whereas none in 8 mg group required a second dose.

Ondansetron lacks the sedative, dysphoric and extrapyramidal symptoms associated with other antiemetics, such as droperidol and metoclopramide[8]. In this study, there were no differences in the incidence of headache and dizziness among the 4 mg groups and 8 mg group. Unlike other antiemetics, ondansetron does not affect mental status to produce these symptoms.

The use of N_2O during laparoscopic procedures has been considered to be an important problem because of its ability to produce bowel distension during the surgery and to increase the incidence of PONV[9]. Recently some authors have found no differences between the groups receiving air and N_2O with respect to the operating conditions, bowel distension or the incidence of PONV[10]. Nevertheless, in our study we use Sevoflurane as an adjuvant anaesthetic associated with infusion of Remifentanil.

Remifentanil is a m-opioid receptor agonist with a context sensitive half-time of 3 min and an elimination half-time £ 10 min. Because of its unique metabolic pathway among this group of drugs, remifentanil represents a new pharmacokinetics class of opioids which is named esterase metabolized opioid (EMO).

Rapid biotransformation to minimally active metabolites should be associated with a short, predictable duration of action with no accumulation of effects on repeated dosing or with continuous infusion. Remifentanil infusion is associated with an age-related reduction in the MAC of isoflurane in humans[11]. Nausea and vomiting may be consequences of remifentanil administration. However, because of its rapid clearance, the incidence of these side effects prove to be less compared with other opioids in some situations. The our study shows an incidence of PONV due to remifentanil, associated with laparoscopic surgery related with an high prevalence of PONV, lower than showed in others studies (14% vs 52% Glaxo-Wellcome studies).

In conclusion we have shown that ondansetron 8 mg is the minimum effective dose for preventing PONV in patients undergoing laparoscopic cholecystectomy with sevoflurane and remifentanil anaesthesia.

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